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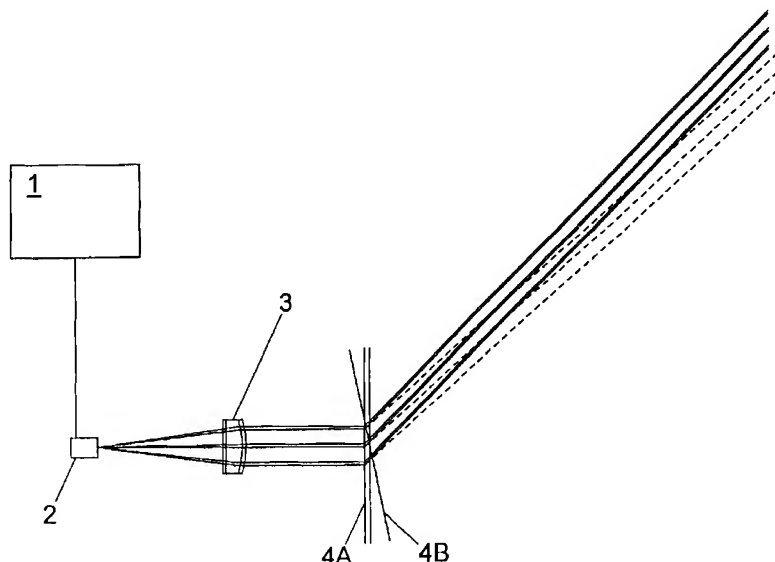
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(54) Title: MOLECULAR RESONANCE STIMULATED BY LOW INTENSITY LASER LIGHT



(57) Abstract: This invention provides an apparatus comprising a laser diode (2) whose wavelength is modulated by an amplitude modulator (1). The laser output is collimated by a lens (3) and passed through an optical element (4) which contains two diffraction gratings spaced by a refractive element. The resulting output contains an interference pattern which can be selected and controlled to interact with chosen molecules so as to induce molecular resonance.

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MOLECULAR RESONANCE STIMULATED BY LOW INTENSITY LASER LIGHT

1 **Molecular Resonance**

2

3 The present invention relates to molecular resonance
4 of molecules, in particular molecular resonance
5 generated by laser radiation.

6

7 The concept of introducing high Q molecules that may
8 be stimulated by laser light to deliver toxic or
9 therapeutic effects is known from Dunlavy US5313315.
10 However, the direct stimulation of natural biological
11 processes by means of molecular resonance using
12 modulated or selective wavelength lasers has hitherto
13 proved to be impossible. This is because of the
14 scattering nature of the medium, the close proximity
15 of many resonances in natural molecules and the
16 difficulty of differentially raising the temperature
17 and thereby the reactivity of individual desired
18 molecules.

19

1 The present invention defines an apparatus and method
2 which overcomes some of these problems and covers the
3 nature and type of molecule susceptible to
4 differential stimulation.

5

6 Many critical chemical reactions in the body are
7 functions of the Cell Surface Cell Adhesion Molecules
8 that are in turn moderated by various integrins. The
9 geometric structure of many Cell Adhesion Molecules
10 and particular integrins is such that they are
11 capable of supporting a resonance at relatively low
12 frequency and surprisingly high Q. Unlike most
13 protein structures which are heavily damped or
14 inherently rigid in structure these molecules
15 generally take the form of a pair of relatively rigid
16 structures separated by space often bridged by a
17 single strand. This structure is especially sensitive
18 to periodic stimulation by a laser source especially
19 when the molecule surface is neutral or slightly
20 negatively charged. The polar and hydrophobic regions
21 of the molecule also differentially absorb energy
22 from laser light. This causes brief alterations in
23 both the structural bond energy and consequently
24 tends to amplify the vibration of the molecule. The
25 effect of this is to slightly increase the chemical
26 reactivity of particular molecules on a cell surface
27 relative to the surrounding molecules of a more
28 generally damped structure or other high Q molecules
29 of a different resonant frequency.

30

1 In vivo the scattering of light at suitable
2 excitation wavelengths is extreme and as a result
3 even quite low frequency modulation signals tend to
4 be corrupted by the multiple scatter path lengths and
5 by the delay in absorption and release of photons in
6 those atoms at low energy states.

7

8 Also if continuous laser radiation is delivered to a
9 mass of cells the high damping factor of the
10 structure means that in general the overall
11 temperature of the cell mass rises. This occurs even
12 if modulated at the resonant frequency of a
13 particular molecule. The use of laser radiation in
14 this way produces an increase in the reactivity of
15 the entire cell surface which means that no actual
16 change in the reaction products occur because the
17 cells are in general, at equilibrium.

18

19 Conversely if very low energy is delivered at the
20 resonance frequency of the cell adhesion molecules or
21 if energy can be delivered as an intermittent pulse
22 of extremely short duration, the cell adhesion
23 molecules and the integrins with their inherently
24 high Q structure tend to maintain a slightly higher
25 temperature than the surrounding molecules. Thus the
26 cell adhesion molecules can be stimulated to a
27 greater reactivity than the surrounding surface
28 molecules.

29

1 Many biological processes can be disturbed into a
2 cascade of increasing reactivity if an initial
3 response is initiated. The immune response is a
4 powerful example of this but the nature of biological
5 reactions on the cell surface means that similar
6 cascade reactions occur for a wide variety of initial
7 conditions disturbed from equilibrium. Thus a very
8 small change in the reactivity of a surface molecule
9 for a short time can result in a dramatic change in
10 the chemistry of the cell surface for a considerable
11 period after the stimulation.

12

13 This effect depends on the cell chemistry being
14 substantially in equilibrium at the commencement of
15 the delivery of the radiation, otherwise the
16 resonance effect will tend to be swamped by the
17 current dominant reaction. Thus the target cells must
18 be in a relatively neutral pH environment and
19 obviously not engaged in a vigorous metabolic
20 process. Ideally also the cell surface molecule would
21 be neutral or slightly negative as this increases the
22 absorption of photons and so increases the transfer
23 of energy from the laser to the molecule.

24

25 Although this limits the use of this method, it has
26 one beneficial effect with respect to therapeutic use
27 in carcinomas. The undifferentiated cells of a
28 carcinoma are generally at equilibrium on the surface
29 as most of the chemical energy of the cell is

1 expended internally in the cell duplication process.
2 This means that the undifferentiated cells of a
3 carcinoma are particularly susceptible to the effect
4 of the method on the surface chemistry since by their
5 nature they conform to the ideal requirements for low
6 energy disturbance of the equilibrium.

7

8 It is a critical requirement of this effect that the
9 initial stimulation is periodic and of very low
10 overall energy, as higher energy stimulation would
11 merely raise the temperature of the entire cell by
12 conduction and would not change the reaction
13 equilibrium. To achieve such a change, individual
14 molecules on the cell surface must be at different
15 temperatures. Ideally it would consist of small,
16 directed bursts of light modulated at the frequency
17 of the desired molecule. Unfortunately it is clearly
18 impossible to direct such a beam in the highly
19 scattering medium of a living human body.

20

21 If a conventional laser or simple light beam is
22 directed at a highly scattering medium, the
23 modulation is eliminated at any substantial frequency
24 because the light paths to any given point are so
25 numerous and of such differing lengths that any
26 modulation is reduced to noise after a few
27 millimetres of the scattering medium. Even at lower
28 frequencies the general level of overall energy
29 delivered to the cells means that conduction and

1 convection tend to raise the overall temperature of
2 the cell surface rather than allow isolated
3 temperature differences to exist for any useful
4 length of time. Further it is impractical to generate
5 a light pulse which is of sufficiently short duration
6 and with a sufficiently high pulse repetition
7 frequency to be of practical use in the stimulation
8 of any resonance of a Q likely to occur in a living
9 cell surface molecule.

10

11 This invention provides a means of differentially
12 stimulating at least those molecules susceptible by
13 their structure to resonant stimulus.

14

15 The invention and preferred features thereof are
16 defined in the appended claims.

17

18 Embodiments of the invention will now be described,
19 by way of example only, with reference to the
20 drawings, in which:

21

22 Fig. 1 is a block diagram of an apparatus
23 embodying the invention;

24 Fig. 2 illustrates an interference pattern
25 produced by the apparatus of Fig. 1;

26 Fig. 3 shows the same interference in a scattering
27 medium;

1 Figs. 4 and 5 show typical cell adhesion
2 molecules;

3 Fig. 6 shows a human integrin molecule with a
4 single substantial high Q resonance;

5 Fig. 7 shows the zinc structure of the GAG protein
6 in the HIV virus; and

7 Fig. 8 shows a typical laser diode spectrum.
8

9 Referring to Fig. 1, the apparatus comprises a laser
10 diode 2 which is controlled by an amplitude modulator
11 1. The laser diode 2 is selected to have a
12 reasonably linear relationship between current and
13 wavelength with minimum mode hopping. The amplitude
14 modulator 1 modulates the current to the laser diode
15 2 which in turn results in a very small wavelength
16 modulation of the laser, for purposes discussed
17 below.

18 The output of the laser diode 2 is collimated by a
19 lens 3 and passed to an optical element 4. The
20 optical element 4 consists of a first diffraction
21 grating, a refractive element, and a second
22 diffraction grating such that the beam is
23 substantially cancelled. A preferred form of the
24 optical element 4 is as disclosed in WO97/22022 (now
25 EP-A1-0865618A and US-A-6064500). This allows the
26 cancellation to occur over a small percentage of the
27 wavelength variance of the laser source, rather than
28 at a single critical wavelength. Wavelengths beyond
29 the acceptance bandwidth of the cancelling optic 4

1 above and below the centre frequency pass without
2 being cancelled. This means that a complex Fresnel /
3 Fraunhofer zone will be generated, defined by the
4 beat frequency of the high and low frequencies as a
5 function of the aperture. This means that relatively
6 sparse zones of constructive interference will occur
7 between the high and low frequency passes of the
8 cancellation element in selected directions from the
9 aperture, as shown in Fig. 2.

10

11 As seen in Fig. 1, the optical element can be
12 adjusted angularly between positions 4A and 4B. This
13 varies the ratio of constructive to destructive
14 interference.

15

16 In effect the continuous beam is transformed into a
17 string of extremely short duration pulses typically
18 of sub femto second duration. The small wavelength
19 modulation of the laser diode 2 causes the
20 constructive and destructive nodes to move rapidly
21 through the volume of the Fresnel zone of the
22 collimator lens aperture. This has the effect of
23 simulating very short (sub picosecond) pulse
24 behaviour at any point in the Fresnel zone through
25 which the nodes pass at a pulse repetition frequency
26 defined by the amplitude modulator frequency.

27

28 The wavelength of the cancellation and constructive
29 interference zones for a theoretical single path

1 would be the difference between the two frequencies.
2 If the bandwidth of the cancelling element is narrow
3 this difference is very small and the effective
4 wavelength of the cancelled / non-cancelled cycle
5 would be very long, of the order of pico-seconds.
6 Therefore, the system would behave substantially
7 similarly to a system with no cancellation because it
8 requires an aperture much larger than the primary
9 light wavelength to generate a useful Fresnel /
10 Fraunhofer zone. Such an aperture would greatly
11 multiply the available Feynman diagram paths
12 eliminating any useful effect, even if it were
13 possible to generate a sufficiently coherent source
14 of such an aperture.

15

16 If the beat frequency can be made high enough the
17 wavelength of the cancelled to non-cancelled cycle
18 can be a fraction of a practical aperture. This will
19 make this wavelength sufficiently small to limit the
20 Feynman paths to within a cycle or two in free space
21 allowing the Fresnel / Fraunhofer effect to be
22 apparent. Since the centre frequency and spectrum
23 spread of a laser diode is easily modulated by
24 adjusting the current and or temperature of the
25 junction, the pattern of the Fresnel / Fraunhofer
26 zones can be varied dramatically by very small
27 variations in the wavelength of one or both pass
28 frequencies. Such modulation is produced in the
29 apparatus of Fig. 1 by the amplitude modulator 2.

30

1 Ideally the diode is modulated only slightly so that
2 the frequencies of the laser spectra move by an
3 amount smaller than that which would cause a second
4 lobe to spill outside the bandpass of the
5 cancellation element. As described above the aperture
6 of the apparatus has a dimension some substantial
7 multiple of the wavelength of the laser and some
8 significantly smaller multiple of the cancellation
9 cycle. Thus the number of different Feynman diagram
10 path lengths will be substantially less than infinite
11 for any given cycle length. Thus as different rays
12 from the laser take slightly different paths through
13 the optical element and thereafter cause the complex
14 Fraunhofer zone within the beam the pattern
15 generated is the inverse of a typical narrow spectrum
16 Fraunhofer zone.

17

18 Therefore, instead of the centre frequencies of the
19 beam being in general uncanceled, the centre
20 frequencies are totally cancelled. Thus instead of a
21 general constant level of light in the beam, the beat
22 frequency beam is characterised by isolated
23 relatively sparse "islands" of constructive
24 interference occurring in the generally cancelled
25 beam. Small variations in the centre frequency of the
26 laser as a result of modulation of the current or
27 temperature of the diode cause these islands of
28 constructive interference to move rapidly within the
29 beam.

30

1 Thus at any given point within the beam path, a
2 constructive interference node can be made to
3 modulate with respect to the modulation frequency of
4 the laser, irrespective of the scattering of the path
5 to that point. This is because few areas of
6 constructive interference exist in the initial beam
7 and while a constructive node can occur at any point
8 which happens to have suitable path lengths through
9 the scattering medium to the source, the initially
10 cancelled portion of the beam can not be
11 reconstructed to become a constructive node at any
12 point. Since the modulation of the laser changes the
13 locations of the constructive nodes at the modulation
14 frequency of the laser the result is that for any
15 point (or more accurately for the substantial
16 majority of points) within the beam a modulation
17 occurs irrespective of the scattering nature of the
18 medium. This is because the probability of a scatter
19 from one sparse node to a region where another sparse
20 node has existed within frequency of the modulation
21 is extremely low.

22

23 In a typical coherent beam, the presence of
24 constructive or destructive interference is of equal
25 likelihood and the modulation of the beam will
26 generally shift one constructive node only to be
27 replaced by another causing any initial modulation of
28 the beam to be swamped by the noise of the multiple
29 paths. In contrast, the limiting factor for the
30 modulation frequency of a sparse constructive

1 interference beam is simply that the overall maximum
2 path length of any substantial probability in the
3 Feynman diagram. Path length is substantially shorter
4 than the wavelength of the modulation.

5

6 For a depth of five or six centimetres in human
7 tissue this allows frequencies in excess of 10 MHz to
8 be successfully modulated and in many human tissues
9 such as bone or neural tissue the depth would be
10 substantially greater or the limiting frequency
11 higher.

12

13 A conventional coherent or incoherent beam would have
14 high probability paths in the Feynman diagram. These
15 paths would overlap at very low frequencies (kHz) and
16 be of little practical use in the stimulation of
17 molecular resonance. It should be noted however that
18 the phenomena described above may be used as a means
19 to multiply the modulation frequency, up to the point
20 where the beam effectively becomes continuous. Thus
21 by careful selection of the aperture, the region of
22 the beam selected for transmission through the medium
23 and the modulation frequency it is possible to cause
24 the constructive nodes to pass across any given point
25 in the beam at frequencies many times higher than the
26 modulation frequency. In ideal conditions the
27 duration of exposure to a constructive node of any
28 point would be for a period equivalent to a quarter

1 of the duration of a wavelength of the molecular
2 frequency repeated once per cycle.

3

4 If the wavelength of the laser is chosen to be one
5 easily absorbed by the atomic structures it is
6 desired to induce to resonance, then the beam will
7 efficiently deliver the desired modulation frequency
8 to the desired molecules. The energy of the beam is
9 extremely low but sufficiently high to differentially
10 raise the temperature of those molecules of
11 sufficient Q. Higher energy intensity would tend to
12 cause sufficient scatter even from the isolated
13 island nodes to swamp the modulation. Again the
14 result would be a general temperature increase rather
15 than the differential temperature increase of the
16 desired molecules.

17

18 Higher intensity can not significantly increase the
19 energy delivered to the desired molecules. Once the
20 probability of a single photon absorption at any
21 point on the molecule in a given and resonant
22 frequency cycle is exceeded, there is little
23 advantage in increasing the intensity since a second
24 photon will scatter without delivering more energy to
25 the given atom structure. The maximum temperature
26 difference that can be induced will be a function of
27 the damping factor and the Q of the resonant
28 component of the molecule. Therefore, increasing the
29 time of stimulation is pointless beyond some

1 reasonable multiple of the known time required to
2 initiate the reaction desired because the maximum
3 possible temperature variance will occur within a few
4 seconds.

5

6 The effect is therefore, only of merit in systems
7 where a small temperature variance can disturb the
8 equilibrium. Naturally this limits the range of
9 molecules that can be stimulated by this method. It
10 is fortunate however that many of the most usefully
11 stimulated molecules have exactly the characteristics
12 required. Most particularly the cell adhesion
13 molecules and integrins mentioned above. It should be
14 noted of course that all biological reactions occur
15 within a narrow temperature range and the progress of
16 most reactions can be varied quite significantly by
17 small temperature differences. It is of course a
18 natural consequence of light stimulation of a
19 molecular resonance that the molecular node
20 temperature of the resonant structure will coincide
21 with the maximum valence state of the atoms since
22 they are in the process of absorbing and emitting
23 photons and so the electrons are in general at a
24 relatively high energy state. Naturally specific
25 photochemical reactions will be favoured and this may
26 either help or hinder the ability of the method to
27 stimulate a specific desired reaction depending on
28 the proximity of unwanted photochemical reaction
29 sites to the resonant stimulated sites. In designing
30 a specific stimulus these factors should be taken

1 into account along with the equilibrium state and the
2 pH.

3

4 As stated above cell adhesion molecules and human
5 integrins such as Alpha 4 Beta 1 are ideally suited
6 for excitation to chemical activity by this method.

7

8 The stimulation of cell adhesion molecules and
9 integrins moderates a number of extremely useful
10 biological processes. Not least of these is cell
11 adhesion itself. It is obviously beneficial to
12 stimulate the adhesion molecules of a carcinoma as
13 the cell adhesion of carcinomas is relatively
14 depressed and enhancing the adhesion serves to reduce
15 the probability of metastasis. Such an effect would
16 be especially beneficial prior to the excision of a
17 tumour, reducing the likelihood of surgically
18 shedding carcinoma cells into the blood or lymph
19 system. The cell adhesion process and the integrins
20 especially Alpha 4 Beta 1 and Alpha 4 Beta 2 are
21 responsible not only for adhesion but also cell
22 recognition.

23

24 Bissel and Weaver have shown that by chemical
25 inhibition of adhesion sites of Alpha 4 Beta1, the
26 cell recognition can be moderated. It is therefore
27 possible to reduce an undifferentiated carcinoma cell
28 to its phenotype by correctly moderating the adhesion
29 reaction. The method used by Bissel and Weaver is

1 practical for in vitro application and can be used as
2 described in their patent for the measurement of
3 response to chemotherapy but it can not practically
4 be used in vivo. Conversely the laser radiation
5 method can be used in vivo and because of the
6 extremely low energies it is inherently safe at least
7 in terms of the radiation used. Care must of course
8 be taken to ensure that the stimulation delivered
9 will have a desirable consequence and much work is
10 needed to determine both the chemical responses that
11 are most easily stimulated and which of those are
12 desirable in a given case.

13

14 Gradually a library of reaction responses susceptible
15 to the stimulation will be developed from theory and
16 experiment and this library will be used to define a
17 range of reactions that are both of clinical use and
18 practical to stimulate. To date we have demonstrated
19 the stimulation of adhesion in leukocytes and neural
20 carcinomas. We have demonstrated substantial
21 moderation of cell surface chemistry in the prostate
22 gland.

23

24 This shows promise in the treatment of various
25 carcinomas. Stimulation of cell adhesion and
26 recognition alters the metabolism of the carcinoma
27 and causes induced, spontaneous apoptosis as a result
28 of undifferentiated cells communicating sufficiently.
29 This in turn causes the natural apoptosis of

1 undifferentiated cells in an undifferentiated
2 environment. We have substantial evidence that like
3 Bissel and Weaver we have observed the reduction to
4 phenotype of undifferentiated cells and leukocytes.

5

6 Wayner US5730978 has shown an integrin-moderated
7 process which suggests that the method may have
8 application in the treatment of auto-immune diseases
9 and in the manipulation of the immune response in
10 general.

11

12 In vitro, the method can be used to alter the
13 chemistry of a variety of proteins and simple amino
14 acid structures in a manner that may be useful in the
15 production of pharmaceutical compounds and nutrition
16 products. Since the polar and hydrophobic components
17 of molecules have substantially different electron
18 populations, Quantum Electrodynamics (QED) shows that
19 these components differentially absorb energy from
20 photons. Coupled with a modulation frequency close to
21 one of the major axes of a given molecule, modulated
22 laser stimulation can be used to increase the
23 homogeneity of a population of proteins or simple
24 amino acid structures. This can be highly
25 advantageous since the metabolic absorption of amino
26 acid structures is moderated in vivo by shape
27 specific enzymes.

28

1 If a simple amino acid nutrient is made homogeneous
2 the number of enzymes required to metabolise the
3 nutrient is reduced. Again the cascade effect of cell
4 chemistry means that such a reduction in the
5 complexity of a particular chemical process can
6 dramatically increase the speed of absorption
7 sometimes by several orders of magnitude since the
8 required enzyme population is far more rapidly
9 manufactured. This is of critical importance in many
10 simple amino acid nutrients since they have a limited
11 life before they are broken down by incidental
12 chemical effects before they can deliver the required
13 effect to the target cells.

14

15 Under ideal conditions it will be possible to order
16 the folding of a protein to the desired biological
17 form by successive stimulation of suitable resonant
18 frequencies and the differential polar and
19 hydrophobic absorption of photons. Again the
20 application of a suitable modulated beam to a
21 sufficient volume of protein by conventional means
22 would be impossible as result of the scattering of
23 the light. The sparse constructive node beam
24 disclosed in the present application makes the
25 delivery of the required modulation a practical
26 possibility. A suitable array of the disclosed sparse
27 constructive node beams could be arranged on a
28 conveyor passing the proteins or simple amino
29 structures sequentially under the various modulation

1 frequencies designed to favour each of the desired
2 folding steps.

3

4 Clearly much research would be required to determine
5 what modulations would be required to produce a
6 desired protein shape and it may be that in practice
7 very few proteins can be usefully manipulated in this
8 way. Such research is not within the scope of this
9 application; rather this application discloses a
10 method and apparatus capable of moderating aspects of
11 the folding process of proteins in a manner that can
12 be applied to a bulk mass for the first time. It is
13 extremely likely that a range of practical protein
14 structures can be generated by this method and it has
15 been shown by experiment that a population of
16 proteins or simple amino structures can be at least
17 made homogeneous which as mentioned above is useful
18 in itself.

19

20 In this regard it should be noted that the rotational
21 polarisation of the light source would cause
22 differential absorption of energy depending on the
23 "handedness" of a given molecular structure. In
24 addition, if the beam is modulated at the resonance
25 of a given structure, it is possible to either
26 enhance the production of one rotation of a molecule
27 versus the other. At slightly higher energy it is
28 possible to cause the destruction by a separate
29 chemical process of one or other rotation by

1 differentiating the temperature and therefore the
2 reactivity of one rotation versus the other. This is
3 a particularly useful application of the method as
4 many drugs and nutrients depend on only one form of
5 the molecule being present.

6

7 In this case of course the maximum Feynman path must
8 be very much shorter and so the maximum depth that
9 rotational polarisation effects would occur would be
10 no greater than a few millimetres in a typically
11 scattering medium. Hitherto no simple practical
12 method has existed to purify a population of
13 molecules to one or other rotation. The method
14 disclosed here provides a means of operating on bulk
15 media to generate a homogeneous single rotation
16 population or to allow a chemical process to
17 preferentially destroy one rotation relative to the
18 other in a mixed population of molecules.

19

20 The chemical consequences discussed herein of
21 molecular stimulation by sparse constructive node
22 techniques result primarily from the repeated
23 acceptance and release of photons by atoms at the
24 resonant frequency of the local atomic bonds or local
25 structure. There is a secondary effect on certain
26 molecular forms such as tetrahedral which can be
27 induced to spin provided the effective pulse length
28 is sufficiently short.

29

1 While the sparse constructive interference beam is
2 the primary thrust of the present application, it is
3 worth noting that the Hamiltonian solution to
4 Maxwell's equations suggest that cancelled light,
5 although carrying no energy in the conventional sense
6 in that it can not interact by conventional Quantum
7 Electrodynamics (QED) processes may have an effect on
8 the permittivity of free space and some theorists
9 suggest an effect on the strong nuclear force.
10 However since it can not scatter by QED effects this
11 has no detrimental affect on the efficiency of the
12 sparse constructive interference modulation and it
13 could be argued that the permittivity and nuclear
14 absorption effect, should it exist, would tend to
15 enhance the efficiency of the modulated frequency
16 coupling to the molecule. It should be noted that the
17 presence of the Hamiltonian effect has never been
18 satisfactorily proven and many theorists discount its
19 existence as a mere mathematical oddity, however we
20 note it here simply to point out that the effect
21 would tend to enhance rather than degrade the benefit
22 of the sparse constructive in interference effect.
23 The apparatus by its nature can therefor be used as a
24 means of delivering such a theoretical modulated
25 Hamiltonian "scalar" wave.

26

27 Figs. 2 to 8 illustrate elements of the foregoing in
28 more detail.

29

1 Fig. 2 shows the sparse constructive interference
2 effect from a 1 percent bandwidth cancellation plate
3 of 5 mm aperture. Black represents constructive
4 nodes.

5 Fig. 3 shows the same sparse constructive
6 interference in a scattering medium showing minimal
7 degradation of the effect and an increased path width
8 of majority destructive interference.

9

10 Figs. 4 and 5 show typical Cell Adhesion Molecules.
11 Both would have two primary resonances a high Q
12 resonance between the main elements at a relatively
13 low frequency and a higher frequency lower Q
14 resonance between the lobes of each element. The
15 molecule in Fig. 4 has a higher frequency resonance
16 between the main elements as it has some backbone
17 structure between the main elements.

18

19 Fig. 6 shows a human integrin molecule which will
20 have a single substantial high Q resonance defined by
21 the mass of the two main elements and the compliance
22 of the single backbone structure between the
23 elements. This molecule is extremely easy to resonate
24 sufficiently to moderate reactions and was the first
25 molecule to be successfully manipulated by the method
26 disclosed. This allowed an in vitro demonstration of
27 cell adhesion stimulated by laser stimulation
28 through a sparse constructive node cancellation
29 optical device. "Tracks" of adhered cell chains could

1 be generated in the beam path of the device in a
2 population of cells with substantially reduced
3 expression of the integrin and generally little
4 adhesion in the absence of the beam.

5

6 Fig. 7 shows the zinc "fingerlike" structure of the
7 GAG protein in the HIV virus. Again the molecule
8 shows the easily resonated dual element with
9 compliant single backbone bridge. This molecule is
10 much smaller and requires a higher energy and
11 resonant frequency. It was successfully resonated
12 with 470nm light using the method disclosed. It
13 should be noted that the chemical conditions around a
14 small viral particle are far harder to control or
15 predict and variable results are to be expected. Even
16 so substantial alterations in the processes of the
17 viral coat were observed and the viral penetration of
18 a cell population could be substantially altered.

19

20 Fig. 8 shows a typical laser diode spectrum, with a
21 typical cancelled portion of the spectrum and the
22 depth of the modulation that can be induced without
23 causing the nodes to spill outside the cancellation
24 zone and complicate the beat frequency pattern.

25 Different laser designs have different resonant modes
26 and these can be selected to obtain the most useful
27 range for a given application. Bragg gratings can be
28 used to stabilise the laser emission line and expand
29 the modulation amplitude that can be used while

1 keeping the overall frequency shift within the
2 required boundary. Lasers can be pulsed with short
3 duration pulses, which will produce an isolated
4 traverse though the frequency mode of the laser and
5 this can be determined to a high degree of
6 repeatability. If a Bragg grating is used with a
7 pulse laser the resulting frequency modulated pulse
8 will have a very high degree of control. The
9 combination of the short laser pulse and the rapid
10 resulting traverse of the sparse constructive nodes
11 means that a given point in the volume in front of
12 the laser will be exposed to extremely short (sub
13 picosecond) duration pulses. There are several
14 applications for such short pulses and conventional
15 methods for short pulse generation are relatively
16 costly.

1 **CLAIMS**

2

3 1. Apparatus for the stimulation of molecular
4 resonance by the application of very low intensity
5 electromagnetic radiation, comprising a laser of
6 multiple line cavity resonance consisting of a laser
7 diode with a collimated or near collimated beam, said
8 beam being passed through a phase cancellation
9 optical element having the characteristic of
10 cancelling several of the central lines of the laser
11 frequency while leaving the higher and lower
12 frequencies generally uncanceled such that the beat
13 frequency of the passed frequencies forms a pattern
14 of interference of constructive and destructive nodes
15 in which the diameter of the beam is set to be a
16 sufficiently low multiple of the wavelength of the
17 beat frequency to allow a substantial Fresnel zone to
18 be apparent in the beam and in which an aperture is
19 provided to select a portion of the Fresnel zone
20 wherein a substantial majority of destructive nodes
21 are apparent relative to the constructive nodes and
22 in which means are provided to modulate the laser
23 frequency.

24

25 2. Apparatus as claimed in Claim 1, wherein the
26 laser frequency is varied by adjusting the current on
27 a laser diode.

28

1 3. Apparatus as claimed in Claim 1 or Claim 2
2 wherein the laser frequency is varied by physical
3 alteration of a secondary cavity such as a crystal
4 provided to double the primary frequency.

5

6 4. Apparatus as claimed in any of the preceding
7 Claims wherein the modulation frequency is a harmonic
8 of the beat frequency.

9

10 5. Apparatus as claimed in any of the preceding
11 Claims wherein the modulation frequency is a harmonic
12 of a specific molecular resonance.

13

14 6. Apparatus as claimed in any of the preceding
15 Claims wherein the aperture or angle of the beam
16 passage through the cancellation device may be varied
17 consequently varying the beat frequency.

18

19 7. Apparatus as claimed in any of the preceding
20 Claims wherein the selected portion of the beam may
21 be varied to alter the balance between constructive
22 and destructive nodes.

23

24 8. Apparatus as claimed in any of the preceding
25 Claims wherein the means for modulating the laser
26 frequency is the consequential mode transition of a
27 laser diode in pulse mode.

1

2 9. Apparatus as claimed in Claim 8 where the laser
3 diode mode is held within bounds by reflection from a
4 Bragg grating so that the modulation of the Fresnel
5 zone nodes is a consequence of the Fourier transform
6 of the pulse.

7

8 10. A method of stimulation of molecular resonance
9 by the application of very low intensity
10 electromagnetic radiation modulated at resonant
11 frequencies of molecules of high Q by use of a laser
12 of multiple line cavity resonance consisting of a
13 laser diode with a collimated or near collimated
14 beam, said beam being passed through a phase
15 cancellation optical element said cancellation device
16 having the characteristic of cancelling several of
17 the central lines of the laser frequency while
18 leaving the higher and lower frequencies generally
19 uncanceled such that the beat frequency of the
20 passed frequencies forms a pattern of interference of
21 constructive and destructive nodes, in which method
22 the diameter of the beam is set to be a sufficiently
23 low multiple of the wavelength of the beat frequency
24 to allow a substantial Fresnel zone to be apparent in
25 the beam and in which an aperture is provided to
26 select a portion of the Fresnel zone wherein a
27 substantial majority of destructive nodes are
28 apparent relative to the constructive nodes and in
29 which means are provided to modulate the laser
30 frequency.

1
2 11. Apparatus for the production of sub picosecond
3 light pulses, the apparatus comprising a laser
4 producing a collimated or near collimated beam, a
5 phase cancellation optical element through which said
6 beam is passed, said phase cancellation optical
7 element being formed by the series combination of a
8 first diffraction grating, a refractive element and a
9 second diffraction grating, whereby a pattern of
10 interference of constructive and destructive nodes is
11 formed in which the diameter of the beam is set to be
12 a sufficiently low multiple of the wavelength of the
13 beat frequency to allow a substantial Fresnel zone to
14 be apparent in the beam, the apparatus further
15 including means for pulsing the laser with short
16 duration pulses to produce for each pulse an isolated
17 traverse through the frequency mode of the laser.
18

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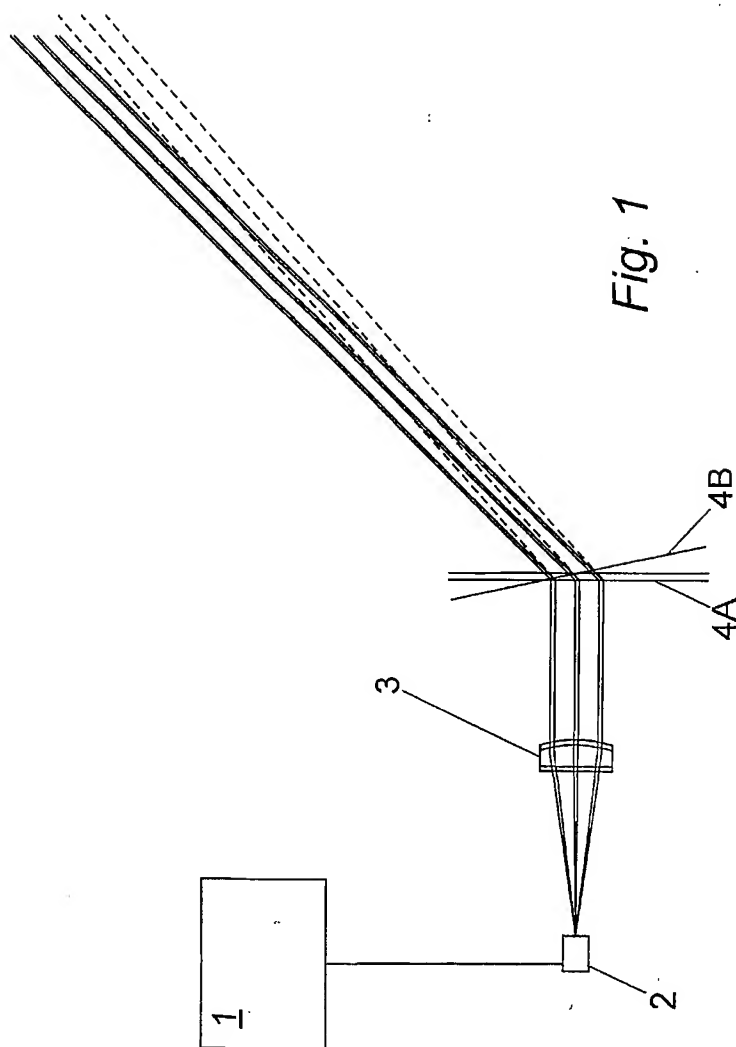


Fig. 1

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Fig. 2



Fig. 3

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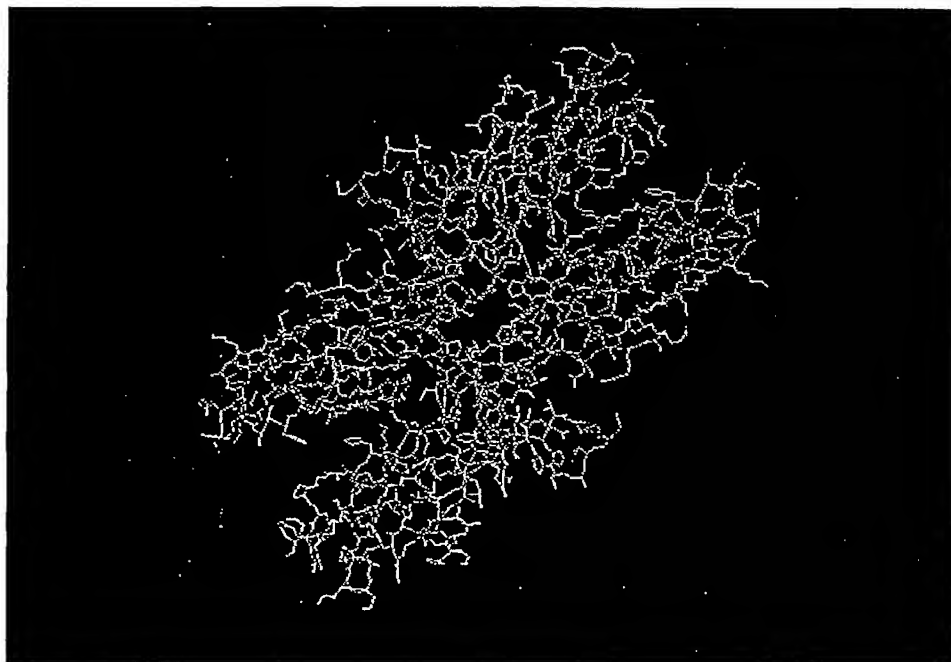


Fig. 4

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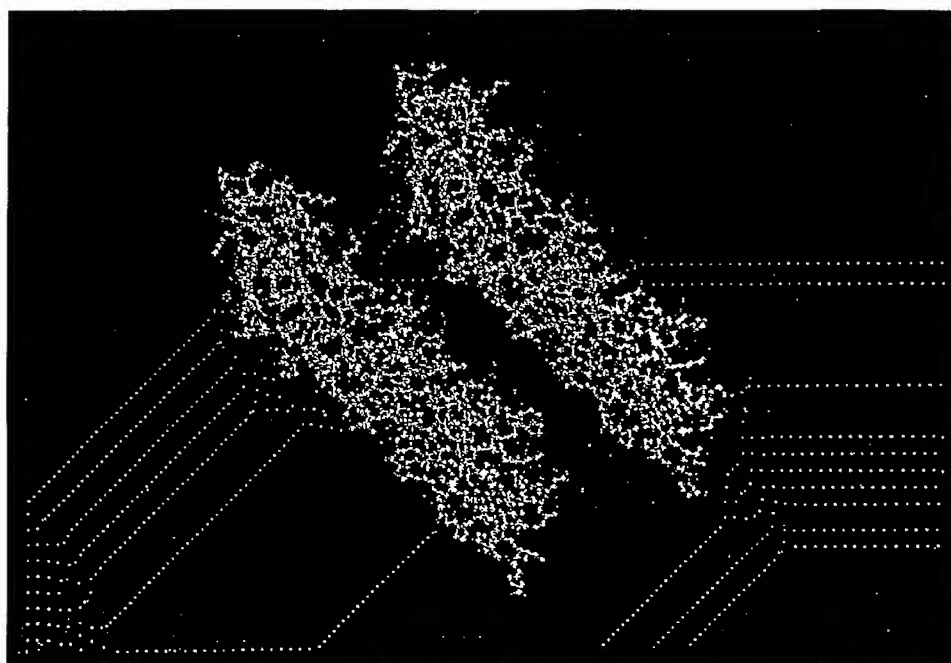


Fig. 5

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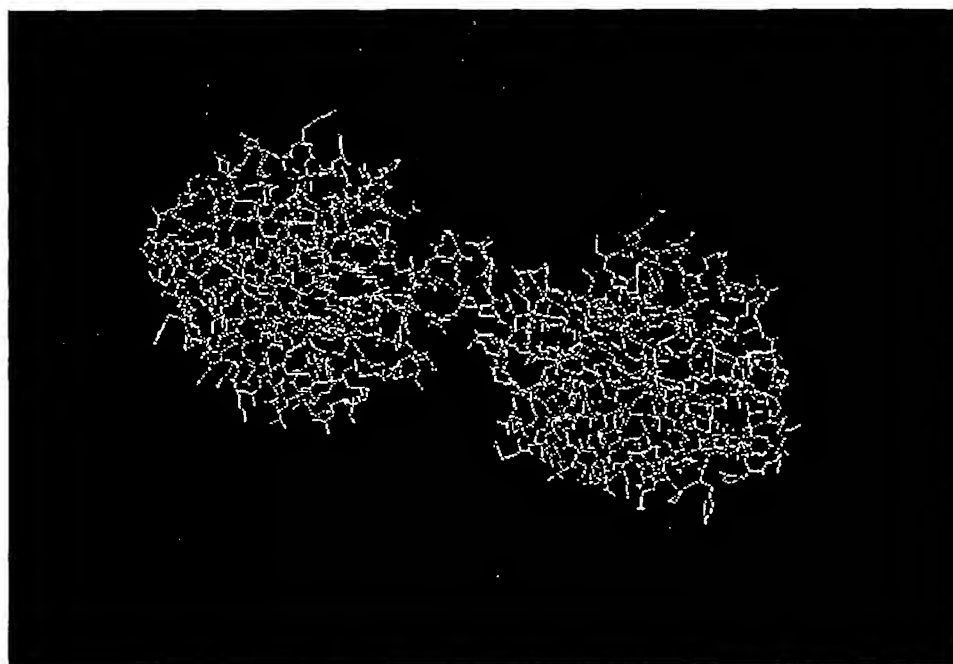


Fig. 6

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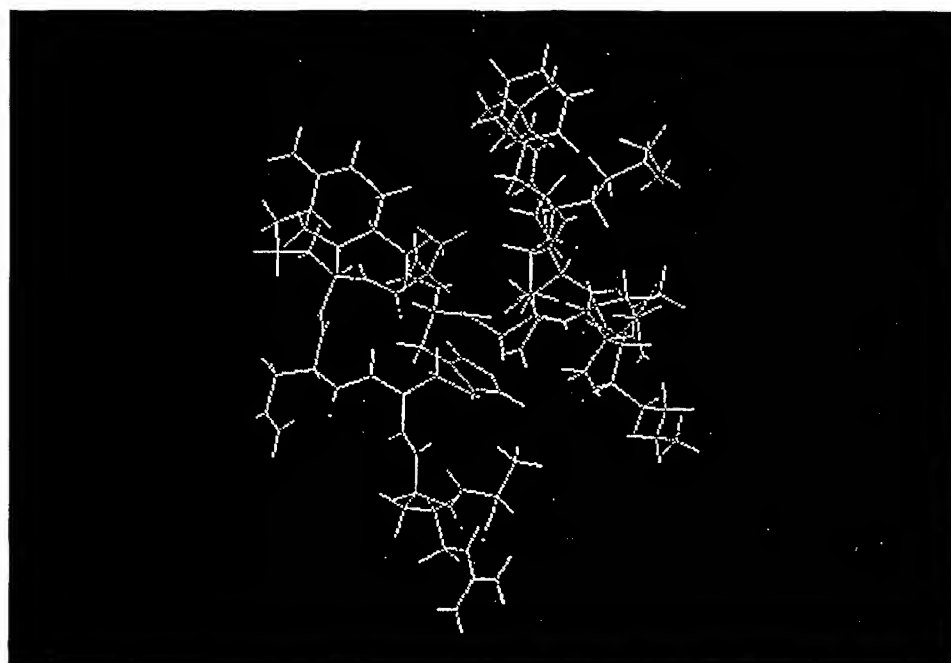


Fig. 7

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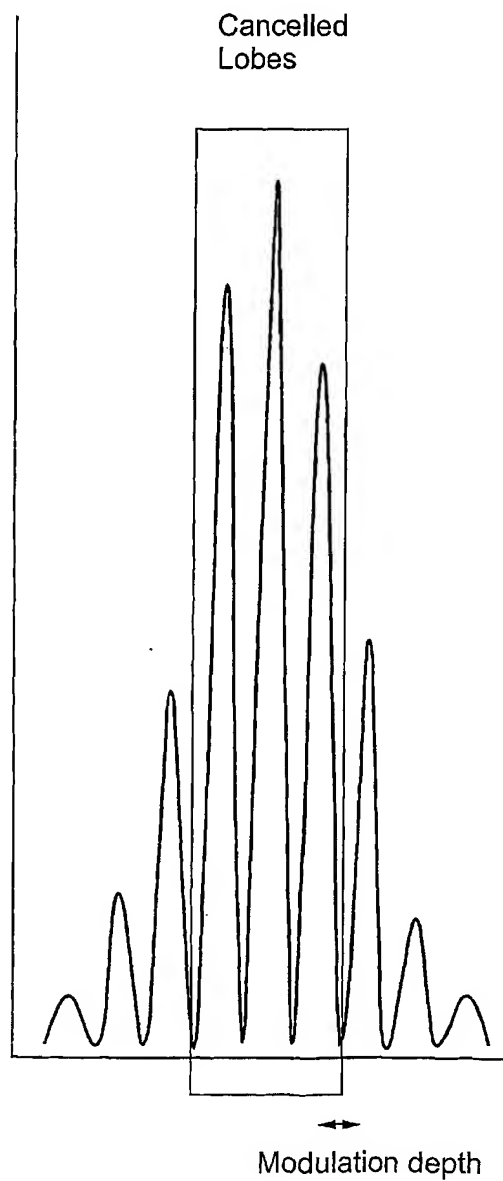


Fig. 8

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/03280

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61N5/067

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61N 602B H01S

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 22022 A (STRACHAN JOHN SCOTT) 19 June 1997 (1997-06-19) cited in the application page 4, line 33 - page 9, line 10 ----	1,10,11
A	US 5 658 234 A (DUNLAVY JOHN HAROLD) 19 August 1997 (1997-08-19) column 2, line 28 - line 67 ----	1
A	US 4 834 474 A (GEORGE NICHOLAS ET AL) 30 May 1989 (1989-05-30) abstract ----	1,10,11
A	US 4 536 883 A (CHAPLINE JR GEORGE F) 20 August 1985 (1985-08-20) column 1, line 32 - line 50 -----	1,10,11

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

5 December 2000

Date of mailing of the international search report

12/12/2000

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 00/03280

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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